

## REMARKS

Examination of claims 5-12, 14-18, 25, and 37-46 is reported in the present Office Action. Claims 5-10, 14-18, 25, 37-42, 45, and 46 were rejected under 35 U.S.C. § 112, first paragraph (scope); claims 5, 10, 25, and 42 were rejected under 35 U.S.C. § 112, first paragraph (written description); Claims 5-9, 16, 17, 34, 37, 38, 42, and 44 were rejected under 35 U.S.C. § 112, second paragraph; Claims 5, 6, 10-12, 14-16, 18, 25, 37, and 39-44 were rejected under 35 U.S.C. § 102(b); claims 5, 17, 25, 38, and 45 were rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed as follows.

### Rejection under 35 U.S.C. § 112, first paragraph (enablement and written description)

Claims 5-10, 14-18, 25, 37-42, 45, and 46 were rejected under § 112, first paragraph for lack of enablement (scope), with the Examiner stating that the specification does not enable the administration of any *Helicobacter pylori* peptide or polypeptide, or any DNA molecule or vaccinal vector encoding such a peptide or polypeptide, for the purpose of preventing or treating *Helicobacter* infection. The Examiner further states that although the previously submitted declarative evidence partially overcame this rejection, it is not commensurate in scope with the invention as claimed, apparently because the claims include within their scope DNA molecules encoding *H. pylori* polypeptides, *H. pylori* peptides, and therapeutic treatment of *H. pylori* infection. In the interest of expediting prosecution, the claims have been amended to specify that which the Examiner has deemed to be enabled: the use of prophylactically effective *H. pylori* polypeptide antigens in methods of inducing a prophylactic immune response, using the specific regimens and routes specified in the claims. Applicants thus respectfully request that this

rejection be withdrawn. Applicants further note that they reserve the right to pursue the previous or similar claims in future, continuation applications.

Claims 5, 10, 25, and 42 were also rejected under § 112, first paragraph on the basis that these claims include subject matter that was not described in the specification in such a way so as to convey to those of skill in this art that the applicants were in possession of the claimed invention at the time the application was filed. This rejection is based upon the inclusion in applicants' claims of references to DNA molecules encoding *Helicobacter* antigens. As is noted above, in the interest of expediting prosecution, claims specifying use of DNA molecules have been canceled, without prejudice. The claimed methods now specify the use of prophylactically effective polypeptide antigens of *H. pylori*. Applicants thus respectfully request that this rejection be withdrawn.

#### Rejections under 35 U.S.C. § 112, second paragraph

Claims 5-9, 16, 17, 34, 37, 38, 42, and 44 were rejected under 35 U.S.C. § 112, second paragraph on several grounds, which are addressed as follows.

The previous rejection of claims 7-9 under § 112, second paragraph as being indefinite has been maintained. This rejection is based on the fact that one type of immune response is recited in the preambles of these claims, while in the body of these claims, more than one type of immune response is noted. As was noted in their previous reply, applicants disagree with this rejection, as the second type of immune response indicated in the bodies of these claims is recited only as a frame of reference in which the type of immune response recited in the claims preambles can be further characterized. Regardless, in the interest of expediting prosecution, these claims have been amended so that the preambles of these claims no longer specify the type

of immune response being induced. Rather, the preambles state that an immune response is induced, and the details as to the types of immune responses induced are present in the bodies of these claims. Applicants thus respectfully request that this rejection be withdrawn.

Claim 5 was rejected for including the term “effective,” on the basis that it is not clear what the amount is effective for. This rejection has been met by the present amendment to claim 5, which now states that a prophylactically effective amount of a prophylactically effective *H. pylori* antigen is employed in the method.

Claims 5 and 6 were rejected for including the phrase “subdiaphragmatic, systemic route,” on the basis that the terms in this phrase are inconsistent with one another. In particular, the Examiner notes that the “subdiaphragmatic” region of the body is limited to the part of a mammal below the diaphragm, while the term “systemic” would include administration to areas that are above the diaphragm. Applicants respectfully request that this rejection be withdrawn.

It is clear that what is meant by the “subdiaphragmatic, systemic” route is administration in a non-mucosal manner in the part of the body below the diaphragm. This is supported, for example, on page 6, throughout which the terms systemic and parenteral are used together. In addition, on page 6, line 28 - page 7, line 1, it is clearly stated that “the administration by the systemic or parenteral route is advantageously carried out in the subdiaphragmatic part of the mammal.” This interpretation of the phrase “subdiaphragmatic, systemic” is also supported in the Examples of the application, which demonstrate administration by such methods.

Claims 16 and 17 have been canceled without prejudice and, thus, the rejection of these claims under § 112, second paragraph is moot.

Claim 34 was rejected in reciting the phrase “in which a ... is co-administered,” with the Examiner suggesting that applicants amend this claim to recite an active step, rather than using

the passive voice. This rejection has been addressed in the manner suggested by the Examiner and, thus, applicants respectfully request that the rejection be withdrawn.

Claims 37 and 38 were rejected for reciting steps in addition to those recited in claim 25, from which claims 37 and 38 depend. The Examiner states that these claims broaden the scope of claim 25, which specifies a particular order of mucosal and parenteral administration steps. Applicants respectfully disagree with this rejection. In particular, claims 37 and 38 do not negate the requirement for a mucosal step followed by a parenteral step, as is specified in claim 25. Rather, these claims add additional steps to the ordered steps of claim 25. To clarify what was intended by these claims, they have each been amended to specify that they are drawn to the method of claim 25 further comprising an additional mucosal (claim 37) or parenteral (claim 38) step. The original mucosal and parenteral steps of claim 25 are not changed by the addition of these steps.

Claims 42 and 44 have been canceled without prejudice and, thus, the rejection of these claims under § 112, second paragraph is moot.

The Examiner notes that the use of the trademarks QS-21, DC-Chol, and Bay should be capitalized and accompanied by generic terminology. The specification has been amended accordingly.

#### Rejections under 35 U.S.C. § 102(b)

Claims 5, 10, 11, 14, and 15 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lee et al. (1995), on the basis that this reference teaches a method of inducing an immune response to an *H. pylori* composition administered subcutaneously. Applicants respectfully request that this rejection be withdrawn because, as is discussed above, the present claims require

that administration take place beneath the level of the diaphragm, and such administration is not mentioned in the Lee reference.

Claims 5, 10, 14, and 15 were also rejected under § 102(b) as being anticipated by Laszlo et al. (1992), on the basis that this reference also teaches a method of inducing an immune response to an *H. pylori* composition administered subcutaneously. Applicants respectfully request that this rejection be withdrawn because, as is discussed above, the present claims require that administration take place beneath the level of the diaphragm, and such administration is not mentioned in the Laszlo reference.

Claims 5, 6, 10, 12, 14-16, 18, 25, 37, and 39-44 were rejected under § 102(b) as being anticipated by WO 96/31235, in light of U.S. Patent No. 6,126,938. This rejection is based on the assertion that the cited reference teaches the administration of an antigen to the dorsolumbar region, which the Examiner states is subdiaphragmatic.

Applicants respectfully request that this rejection be withdrawn. In particular, applicants note that claim 5, from which claims 6, 10, 12, 14-16, and 18 depend, has been amended to specify that the method consists essentially of subdiaphragmatic, systemic administration, thus excluding the use of additional administration routes in the method. The cited reference describes the use of dorsolumbar administration in the context of a method requiring also nasal and/or buccal administration (column 4, lines 60-65) and administration by an additional mucosal route (column 4, line 66 - column 5, line 7). Thus, the cited reference does not describe the invention of claims 5, 6, 10, 12, 14-16, and 18, and the rejection should be withdrawn with respect to these claims.

This rejection should also be withdrawn with respect to claims 25, 37, and 39-44, as these claims require administration by a mucosal route, followed by a parenteral route, and the cited

reference nowhere describes such a method. Rather, the passage referred to in the Office Action as supporting this rejection (column 7, lines 44-50) simply specifies that administration by the nasobuccal route is combined with systemic administration, but does not specify the particular order required by the present claims. Applicants also note that claim 40 requires that the mucosal administration step of claim 25 be oral, and the reference certainly does not mention administration by such a route, followed by parenteral administration. Applicants thus respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 5, 17, 25, 38, and 45 were rejected under § 103(a) for obviousness over Guy et al., WO 96/31235, which is in the French language, in light of Guy et al., U.S. Patent No. 6,126,938, the English language specification of which corresponds to that of WO 96/31235, in view of Thomas, Jr. et al. (U.S. Patent No. 5,919,463). This rejection is respectfully traversed.

The Examiner states that the Guy reference differs from the rejected claims by failing to show the combination of an *H. pylori* antigen and a *C. difficile* adjuvant. Applicants respectfully disagree. As is discussed above, claim 5 (and thus dependent claim 17) specifies a method that consists essentially of subdiaphragmatic, systemic administration, and the Guy reference does not describe or provide motivation to carry out such a method. Rather, the methods described in the Guy reference require the use of at least two routes of administration and provides no basis to believe that use of only one route, and in particular that specified by these claims, would be effective. The Thomas reference also does not provide such a suggestion or motivation. Rather, the main focus of the Thomas reference is the use of *C. difficile* toxins as mucosal adjuvants, and

the reference provides no motivation or suggestion to use such toxins as adjuvants in subdiaphragmatic administration methods such as those now claimed.

This rejection should also be withdrawn with respect to claim 25 (and dependent claims 38 and 45), because, as is discussed above, the Guy reference does not teach the use of a method involving mucosal administration followed by parenteral administration, and does not provide any motivation to carry out such a method. Indeed, the entire focus of the Guy reference is the identification of other effective immunization routes. The Thomas reference also fails to even mention methods involving mucosal followed by parenteral administration. Applicants thus respectfully request that this rejection be withdrawn.

Claims 5, 17, 25, 38, and 45 were also rejected under § 103(a) for obviousness over the Guy reference, in view of Lee (U.S. Patent No. 5,837,240). The Examiner states that the teachings of the Guy reference differ from the present claims by failing to show the combination of an *H. pylori* antigen with LT or CT adjuvants, and the administration of an *H. pylori* antigen by the parenteral route more than once.

Applicants respectfully disagree with this rejection. As is discussed above, claim 5 (and thus dependent claim 17) specifies a method that consists essentially of subdiaphragmatic, systemic administration, and the Guy reference does not describe or provide motivation to carry out such a method. Rather, the methods described in the Guy reference require the use of at least two routes of administration and provides no basis to believe that use of only one route, and in particular that specified by these claims, would be effective. The Lee reference also does not provide such a suggestion or motivation. Rather, the main focus of the Lee reference is the use CT and LT with as parenteral adjuvants in *H. pylori* immunization methods, and the reference

provides no motivation or suggestion to use such toxins as adjuvants in subdiaphragmatic administration methods such as those now claimed.

This rejection should also be withdrawn with respect to claim 25 (and dependent claims 38 and 45), because, as is discussed above, the Guy reference does not teach the use of a method involving mucosal administration followed by parenteral administration, and does not provide any motivation to carry out such a method. Indeed, the entire focus of the Guy reference is the identification of other effective immunization routes. The Lee reference also fails to even mention methods involving mucosal followed by parenteral administration. Applicants thus respectfully request that this rejection be withdrawn.



CONCLUSION

Enclosed is a Notice of Appeal, a Petition to extend the period for replying to the Office Action for three months, to and including March 5, 2003, and payment of the corresponding appeal and extension fees. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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## Version of Amendment with Markings to Show Changes Made

The specification has been amended as follows.

Page 9, lines 15-25:

The cationic lipids are also known and are commonly used as transporting agents for polynucleotides. There may be mentioned for example Lipofectin<sup>TM</sup> also known by the name DOTMA (N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride), DOTAP (1,2-bis(oleyloxy)-3-(trimethyl-ammonio)propane), DDAB (dimethyldioctadecylammonium bromide), DOGS (dioctadecylamidoglycyl spermine), and cholesterol derivatives, such as DC-CHOL [DC-chol] (3-beta-(N-(N',N'-dimethylaminoethane) carbamoyl) cholesterol). A description of these lipids is provided by EP 187,702, WO 90/11092, U.S. Patent No. 5,283,185, WO 91/15501, WO 95/26356, and U.S. Patent No. 5,527,928. The cationic lipids are preferably used with a neutral lipid such as DOPE (dioleoylphosphatidylethanolamine) as is, for example, described in WO 90/11092.

Page 13, lines 16-26:

Useful liposomes for the purposes of the present invention can be selected in particular from pH-sensitive liposomes, such as those formed by mixing cholesterol hemisuccinate (CHEMS) and dioleoyl phosphatidyl ethanolamine (DOPE); liposomes containing cationic lipids recognized for their fusogenic properties, such as 3-beta-(N-(N',N'-dimethylaminoethane)carbamoyl)cholesterol (DC-CHOL [DC-chol]) and its equivalents, which are described in U.S. Patent No. 5,283,185 and WO 96/14831, dimethyldioctadecylammonium bromide (DDAB) and the BAY compounds described in EP 91645 and EP 206 037, for example BAY R1005 [Bay R1005] (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate; and liposomes containing MTP-PE, a lipophilic derivative of MDP (muramidyl dipeptide). These liposomes are useful for adding as adjuvant to all the immunogenic agents cited.

Page 13, line 27 - page 14, line 2:

Useful ISCOMs for the purposes of the present invention can be selected in particular from those compounds of QuilA or of QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) combined with cholesterol and optionally also with a phospholipid such as phosphatidylcholine. These are particularly advantageous for the formulation of the lipid-containing antigens.

Page 14, lines 18-23:

A useful adjuvant for the purposes of the present invention can also be a fraction derived from the bark of the South American tree *Quillaja Saponaria Molina*; for example, QS-21, a fraction purified by HPLC chromatography as is described in U.S. Patent No. 5,057,540. Since some toxicity may be associated with QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*), it may be advantageous to use the latter in liposomes especially based on sterol, as is described in WO 96/33739.

Page 19, lines 23 and 24:

Other compounds, such as MPLA, PLGA, [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol), and QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) can also be used as adjuvants for the mucosal route.

Page 21, lines 6-11:

Figure 3 refers to Example 1 and presents the levels of urease activity after a challenge, measured 4 hours after sacrificing mice which have received 3 times, on D0, D28, and D56: (a) a urease preparation encapsulated at about 80% in [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol) liposomes, in the dorsolumbar muscles; or (b) a urease preparation with cholera toxin adjuvant, by the intragastric route. Experiments (c) and (d) correspond respectively to the positive and negative controls.

Page 21, lines 12-17:

Figure 4 refers to Example 1 and presents the levels of urease activity after a challenge measured 4 hours after sacrificing mice which have received 3 times, on D0, D28, and D56: (a) a urease preparation with cholera toxin adjuvant, by the intragastric route or (b) a urease preparation with QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) adjuvant, by the subcutaneous route in the left posterior sublumbar part. Experiments (c) and (d) correspond respectively to the positive and negative controls.

Page 22, lines 2-10:

Figures 6A and 6B show the urease activity (Figure 6A) measured after 4 hours (OD<sub>550</sub> nm) using the Jatrox test (Procter & Gamble) and the bacterial load in mice infected with *H. pylori* and then submitted to various treatments A - H [A: LT + urease, orally; B: QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) + urease, parenterally in the neck; C: QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) + urease, parenterally in the lumbar region; D: QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) alone, sub-cutaneously in the lumbar region; E: [Bay R1005] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyl dodecanoylamide acetate + urease, parenterally in the neck; F: Bay R1005 + urease, parenterally in the lumbar region; G: [Bay R1005] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyl dodecanoylamide acetate alone, sub-cutaneously in the lumbar region (control); H: saline, sub-cutaneously in the lumbar region (positive control)]. I represents the negative control.

Page 22, line 20 - page 23, line 1:

Figure 8 shows the effect of urease immunization on experimental challenge of rhesus monkeys with *H. pylori*. Monkeys were immunized with urease by parenteral routes (100 µg urease + 1 mg alum or 800 µg [Bay] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyl dodecanoylamide acetate) or by a mucosal prime (orally administered 4 mg urease + 100 µg LT)/parenteral boost (urease + alum) strategy with 3 doses administered every 3 weeks followed by a fourth dose administered 20 weeks after the first priming dose. Monkeys were challenged one week after the last booster dose. The monkeys

were euthanized 10 weeks after challenge, 10 punch biopsies per animal were harvested from the stomach and cultured to determine *H. pylori* colonization. Each symbol above represents the mean CFU of 10 sites cultured per monkey. The line represents the median CFU for the treatment group.

Page 25, lines 5-23:

[DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol) liposomes containing urease are prepared as follows: first of all, to obtain a dry lipid film containing 100 mg of [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol) (R-Gene Therapeutics) and 100 mg of DOPC (dioleoylphosphatidylcholine) (Avanti Polar Lipids), these products are mixed in powdered form in about 5 ml of chloroform. The solution is allowed to evaporate under vacuum using a rotary evaporator. The film thus obtained on the walls of the container is dried under high vacuum for at least 4 hours. In parallel, 20 mg of a urease lyophilisate and 100 mg of sucrose are diluted in 13.33 ml of 20 mM Hepes buffer pH 7.2. Ten ml of this preparation (which contains 1.5 mg of urease and 0.75% sucrose) is filtered on the 0.220 µm Millex filter and then used to rehydrate the lipid film. The suspension is stirred for 4 hours and then either extruded (10 passes on a 0.2 µm polycarbonate membrane) or microfluidized (10 passes at a pressure of 500 kPa in a Microfluidics Co Y10 microfluidizer). In the liposome suspension thus obtained, the level of encapsulated urease is from 10 to 60%. This suspension is lyophilized after having adjusted the sucrose concentration to 5% (425 mg of sucrose are added per 10 ml). Before use, the lyophilisate is taken up in an appropriate volume of water or buffer and the suspension is purified on a discontinuous sucrose gradient (steps of 0, 30, and 60%) so as to obtain a preparation in which the quantity of encapsulated urease is greater than about 70% compared with the total quantity of urease.

Page 25, lines 26 and 27:

The QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) (Cambridge Biosciences; Aquila) is used as adjuvant in an amount of 15 µg/dose of urease.

Page 28, lines 18-20:

Figure 3 shows that a urease preparation encapsulated into [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol) liposomes and administered by the subcutaneous route in the sublumbar region gives results as good as those obtained in the standard reference experiment.

Page 30, lines 22-25:

The *E. coli* heat-labile toxin (LT) (Sigma) or the B subunit of the cholera toxin (CTB) (Pasteur Mérieux sérums & vaccins) was used as mucosal adjuvant whereas [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol) was used as parenteral adjuvant. [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol) powder is simply rehydrated with an antigen preparation.

Page 33, line 28 - page 34, line 12:

OF1 mice were infected with  $10^6$  colony-forming units (cfu) of the *H. pylori* strain ORV2001. After one month, verification that the infection was well-established was made by randomly sacrificing 10/100 mice and testing the urease activity on a quarter of the entire stomach. Since all of the results were positive, the mice were then immunized (10 per group) 3 times at 3 weekly intervals, either subcutaneously using 10 µg of recombinant urease supplemented with 15 µg of QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*) (Aquila) or 400 µg of adjuvant [Bay R1005] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate) (Bayer), or orally using 40 µg of urease mixed with 1 µg of LT. For each of the two adjuvants administered parenterally, the immunization was carried out either in the neck, in order to reach the lymphatic ganglions of the upper region of the body, or in the lumbar region, in order to reach the abdominal lymphatic ganglions. Ten mice were left uninfected and unimmunized (negative control), whereas the mice of the positive control received a saline solution, QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*), or [Bay] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate) adjuvant subcutaneously (lumbar region).

Page 34, lines 13-23:

One month after the third immunization, all of the mice were sacrificed and the stomachs removed to evaluate the extent of the colonization by measuring the urease activity (10/10 mice were analyzed in each group), as well as by carrying out quantitative culturing (5/10 were analyzed). Figures 6A (test relating to urease) and 6B (culturing) show that in the mice immunized with urease supplemented with QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*), subcutaneously in the lumbar region, the infection had virtually disappeared (4/5 mice were negative in quantitative culturing). The mice immunized with urease subcutaneously in the neck, in the presence of QS-21 (purified fraction of saponin extracted from *Quillaria Saponaria Molina*), and the mice that received urease plus LT orally exhibited a 10- to 100-fold decrease in the infection when compared with the unimmunized mice. The [Bay] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate) adjuvant induced an identical decrease, which was more pronounced in the mice immunized in the lumbar region.

Page 37, lines 2-8:

In contrast to the monkeys receiving the mucosal prime/parenteral boost regimen, monkeys immunized by the parenteral route with urease + [Bay] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate) showed no difference in *H. pylori* colonization compared with the sham-immunized controls ( $p = 1.00$ ), while monkeys treated with urease + alum showed a partial effect ( $p=0.33$ ) (Figure 8). Culture data was unavailable for one of the monkeys in the group receiving urease + [Bay] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate), due to heavy contamination of gastric samples with other bacteria.

In the Claims:

Claims 5, 7- 9, 25, 37, 38, 45, and 46 have been amended as follows.

5. (Twice Amended) A method of inducing a [protective or therapeutic] prophylactically effective immune response against *Helicobacter* in a mammal, said method [comprising] consisting essentially of administering to said mammal [an effective amount of] a prophylactically [or therapeutically] effective amount of a prophylactically effective *Helicobacter pylori* polypeptide antigen by the subdiaphragmatic, systemic route.

7. (Amended three times) The method of Claim 6, further comprising induction of a Th2-type immune response, wherein the [in which the Th1-type] immune response of said mammal is characterized by either (i) [by] a ratio of the ELISA IgG2a:IgG1 titers greater than or equal to 1:100, or (ii) [by] a ratio of the ELISA IgG2a:IgA titers greater than or equal to 1:100.

8. (Twice Amended) The method of Claim 7, in which the [Th1-type] immune response of said mammal is characterized either (i) by a ratio of the ELISA IgG2a:IgG1 titers greater than or equal to 1:10, or (ii) by a ratio of the ELISA IgG2a:IgA titers greater than or equal to 1:10.

9. (Twice Amended) The method of Claim 8, in which the [Th1-type] immune response of said mammal is characterized either (i) by a ratio of the ELISA IgG2a:IgG1 titers greater than or equal to 1:2, or (ii) by a ratio of the ELISA IgG2a:IgA titers greater than or equal to 1:2.



25. (Twice Amended) A method of [preventing or treating] inducing a prophylactically effective immune response against *Helicobacter* infection in a mammal, said method comprising in order the steps of:

mucosally administering [an effective amount of] a prophylactically [or therapeutically] effective amount of a prophylactically effective *Helicobacter pylori* antigen to said mammal; and then

parenterally administering a prophylactically effective amount of a prophylactically effective *Helicobacter pylori* antigen to said mammal.

37. (Amended) The method of claim 25, further comprising carrying out [in which] more than one mucosal administration [is carried out].

38. (Amended) The method of claim 25, further comprising carrying out [in which] more than one parenteral administration [is carried out].

45. (Amended) The method of Claim 25, further comprising mucosally co-administering [in which] a mucosal adjuvant selected from the group consisting of *Escherichia coli* heat labile enterotoxin (LT), cholera toxin (CT), *Clostridium difficile* toxin, *Pertussis* toxin (PT), and combinations, subunits, toxoids, and mutants derived therefrom[, is co-administered] with the mucosally administered *Helicobacter pylori* antigen.

46. (Amended) The method of Claim 25, in which a parenteral adjuvant selected from the group consisting of alum, QS-21 (purified fraction of saponin extracted from *Quillaja*

Saponaria Molina), [DC-chol] DC-CHOL (3-beta-(N-(N',N'-dimethylamino-ethane)carbamoyl)cholesterol), and [Bay] BAY R1005 (N-(2-deoxy-2-L-leucylamino-beta-D-glucopyranosyl)-N-octa-decyldodecanoylamide acetate) is co-administered with the parenterally administered *Helicobacter pylori* antigen.